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## Potential neurovirulence of common cold virus

An elegant recent study by Thomas Dufresne and Matthias Gromeier<sup>1</sup> suggests that a causative agent of the common cold, coxsackievirus A21 (CAV21), is potentially neurovirulent and could, under the right circumstances, cause a poliomyelitis-like illness. CAV21 and poliovirus are members of the enterovirus genus (family *Picornaviridae*) and show remarkable genetic similarity.<sup>2</sup> However, CAV21 causes upper respiratory-tract infections whereas poliovirus causes neurological disease including poliomyelitis, which clinically manifests as acute flaccid paralysis. The contrast in clinical presentation has been attributed to the different receptors used for cell invasion: intercellular adhesion molecule-1 (ICAM-1) is the receptor for CAV21 and CD155 is the receptor for poliovirus. Not surprisingly, the genomes of these two related viruses show the greatest dissimilarity in the capsid (or viral coat) region.<sup>3</sup>

Murine ICAM-1 does not support CAV21 binding and mice are not normally susceptible to infection with this virus. Dufresne and Gromeier<sup>1</sup> stably inserted the gene encoding human ICAM-1 (hICAM-1) into the genome of a mouse (which thus became transgenic), resulting in expression of hICAM-1 by the animal's cells. They then inoculated one gastrocnemius muscle of the transgenic mouse with CAV21. Acute flaccid paralysis developed in the injected muscle, but not in any other muscle. CAV21 replication, motorneuron destruction, and inflammation were detected in the ipsilateral anterior horn of the spinal cord, but viral replication was not seen in the injected muscle. The abnormalities in the spinal cord did not occur if the sciatic nerve was transected before inoculation (figure). These observations suggest that CAV21 can be pathogenic for motorneurons and that this neurovirulence is dependent on invasion of the central nervous system by retrograde transport along nerve axons.

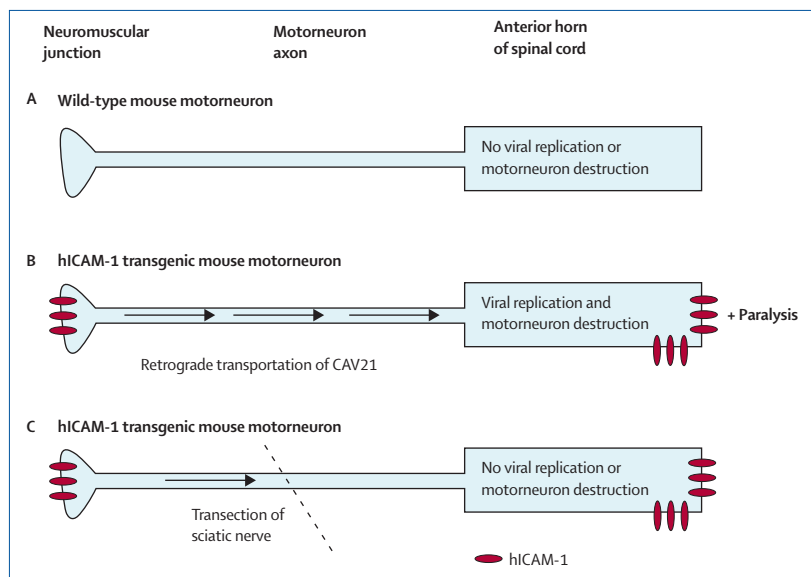
These findings are scientifically important because they suggest that CAV21 has all the machinery required to cause a poliomyelitis-like illness, but is prevented from doing so by virtue of its receptor not being expressed at the neuromuscular junction. Dufresne and Gromeier<sup>1</sup> found low levels of hICAM-1 at the neuromuscular junction of hICAM-1 transgenic mice, but not in wild-type mice. Unfortunately, they did not report whether there is hICAM-1 expression at the human neuromuscular junction, so leaving doubt as to how the observations translate to human beings. They also found hICAM-1 expression on motorneurons in the spinal cord of transgenic mice, but no paralysis occurred when CAV21 was injected directly into the central nervous system. This apparently paradoxical observation could be explained

by a requirement for neuronal infection of a co-receptor that is expressed at the neuromuscular junction, but not by neurons in the central nervous system. A role has been found for decay accelerating factor as a coreceptor for CAV21 attachment to human cell lines<sup>4</sup> and, indeed, decay accelerating factor is expressed at the neuromuscular junction,<sup>5</sup> but could not be found on neurons in the central nervous system.<sup>6</sup>

2004 sees the 50<sup>th</sup> anniversary of Enders, Weller, and Robbins receiving the Nobel Prize in Medicine for culturing poliovirus,<sup>7</sup> and the year coincides with the final stages of the Global Polio Eradication Programme. How clinically significant is the discovery of neurovirulent potential for CAV21 from a public-health perspective and should it concern us? Dufresne and Gromeier<sup>1</sup> chose to refer to the acute flaccid paralysis observed with CAV21 infection in hICAM-1-transgenic mice as "poliomyelitis". In line with WHO definitions, we think this term is best reserved for poliovirus and that "poliomyelitis-like illness" should be used for acute flaccid paralysis caused by other agents.<sup>8</sup> Thus poliomyelitis eradication is not directly affected by Dufresne and Gromeier's findings, but their results increase our concern that the global public-health burden of acute flaccid paralysis will not disappear with the eradication of poliovirus.

Several reasons suggest that CAV21 itself is unlikely to be a clinically significant cause of poliomyelitis-like illness in human beings. CAV21 infection in the hICAM-1 transgenic mice is site-restricted and much less aggressive than poliomyelitis in human beings. Paralysis only occurred in the hICAM-1 transgenic mice via the intramuscular route and not with intravenous, intranasal, or central nervous system routes, and paralysis remained localised to the injected muscle. This observation is analogous to "provocation poliomyelitis" where skeletal muscle injury predisposes an individual to poliomyelitis from concurrent poliovirus infection.<sup>9</sup> Unlike CAV21 in hICAM-1 transgenic mice, poliovirus can spread to the central nervous system directly in the context of viraemia, as well as via retrograde axonal transport. In addition, poliovirus usually enters human beings via the oral route and not by the direct intramuscular route. Dufresne and Gromeier<sup>1</sup> did not report the result of oral administration of CAV21 in hICAM-1 transgenic mice.

What could account for the difference in severity between CAV21-induced poliomyelitis-like illness and poliomyelitis? The most likely answer is differences in binding of viral capsid with either hICAM-1 or CD155 and the tissue distribution of these receptors and any relevant co-receptors, such as decay accelerating factor. CAV21 could present more of a threat to



**Figure:** Motorneuron innervating gastrocnemius muscle in three mice from experiments by Dufresne and Gromeier<sup>1</sup>

human beings if it successfully switched its receptor specificity from hICAM-1 to CD155 and developed into a new polio-like virus. How likely is this? It has been suggested that this process would be more likely in the face of poliovirus eradication.<sup>10</sup> RNA viruses such as the enteroviruses have extremely high mutation frequencies and exist as a mixture of slightly different viruses or quasispecies, allowing rapid evolution.<sup>11</sup> Nevertheless, wild-type poliovirus has been absent from many countries for years and no obvious replacement of poliovirus with CAV21 has emerged.

It is important to appreciate that various viruses are recognised causes of poliomyelitis-like illness, including flaviviruses such as Japanese encephalitis and West Nile virus.<sup>8</sup> Several enteroviruses can cause poliomyelitis-like illness, and so it is possible that CAV21 occasionally causes a poliomyelitis-like illness, although this has never been described. To a certain extent, human enterovirus 71 has already made a bid to occupy the biological niche vacated by poliovirus. Human enterovirus 71, which is thought to enter cells via the receptor for neuron growth factor,<sup>12</sup> causes neurological disease, including poliomyelitis-like illness, as well as hand-foot-and-mouth disease. Although first discovered in 1969, there has been a significant increase in epidemic activity for human

enterovirus 71 in the Asia-Pacific region since 1997, with outbreaks in Malaysia, Taiwan, Singapore, and Australia.<sup>13</sup>

The neurovirulent potential of CAV21 seen by Dufresne and Gromeier<sup>1</sup> using a mouse transgenic for hICAM-1 is an interesting scientific finding and sheds new light on the pathogenesis of viral infections in the nervous system. At present, it seems unlikely that CAV21 will present a major threat to public health.

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## Strokes and holes and headaches: are they a package deal?

The relation between patent foramen ovale (PFO) and systemic embolisation, especially transient ischaemic attack or stroke, has attracted considerable interest over the past decades<sup>1</sup> because of the increasingly widespread application of diagnostic echocardiography and now transcranial

doppler ultrasound. The possibility that a young woman had a clot pass through a PFO and cause a fatal stroke was suggested in 1877.<sup>2</sup> In 1881, Zahn reported systemic embolisation through a PFO in a woman with uterine thrombi;<sup>3</sup> he added “paradoxical embolism” to the medical